Familial risks for eye melanoma and retinoblastoma: results from the Swedish Family-Cancer Database

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No systematic population-based studies have been conducted on familial eye cancers. Reliable data on familial risks are important for clinical counselling and cancer genetics. The current analysis was based on the nation-wide Swedish Family-Cancer Database on 10.5 million individuals, containing families with parents and offspring. Cancer data were retrieved from the Swedish Cancer Registry from the years 1958 to 2002, including 3636 patients with any type of eye cancer. Familial risk for offspring was defined using the standardized incidence ratio (SIR), adjusted for many variables. Ocular melanoma was detected in two parent–offspring pairs, but the SIR of 3.90 was not significant. Parental upper aerodigestive tract (2.05), left-sided colon (1.83) and male non-medullary thyroid (6.98) cancers showed an association with ocular melanoma, albeit some with a borderline significance. The SIR for leukaemia was increased when parents were diagnosed with eye melanoma. There was no evidence for the association of ocular melanoma with cutaneous melanoma. The SIR for ocular melanoma was 1.76 when a sister was diagnosed with breast cancer, but there was no increase when a mother was diagnosed with breast cancer. When both a child and the parent presented with retinoblastoma, the SIR was 900. The parents of children with retinoblastoma had an excess of small intestinal and rectal cancers and Hodgkin's disease. The present findings were based on a limited number of cases, but they display a complex and heterogeneous pattern of familial associations in ocular melanoma, including an association with breast cancer through a putative recessive mechanism. *Melanoma Res* 16:191–195 © 2006 Lippincott Williams & Wilkins.

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Introduction

Eye neoplasms [*International Classification of Diseases*, 7th Revision (ICD-7): code 192] include melanomas as the most common histological type (close to 80%), followed by retinoblastoma (over 5%), unclassified tumours (5%) and gliomas (less than 5%), in the Swedish Cancer Registry. Most of the tumours are intraocular. Heritable forms of retinoblastoma are caused by mutation in the *RB1* gene, resulting in tumours in early childhood and a risk of second tumours [1–3]. Ocular melanoma is associated with fair skin, an abundance of naevi and frequent sunburn, suggesting a role for ultraviolet radiation [4–6]. However, the incidence trends for ocular and cutaneous melanoma are entirely different: the former has been stable in Sweden during the past 40 years, but the latter has increased some eight-fold [7]. Molecular genetic studies on ocular melanoma have been largely exclusionary [8]. The coexistence of ocular and cutaneous melanomas in some patients suggests a predisposition to both types, but mutations in the *p16* (*CDKN2A*) gene do not appear to be involved [8–10]. An association between ocular melanoma and breast and/or ovarian cancers has also been observed, and the data from breast cancer families have implicated *BRCA2* as a predisposing gene [11]. However, in view of the more recent results, the role of *BRCA2* sequence variants, if any, is small, and other genes predisposing to ocular melanoma with and without association to breast cancer may yet be found [8]. The rarity of ocular melanomas is a limiting factor in all types of aetiological studies. For example, a previous study on ocular melanoma from the Swedish Family-Cancer Database did not identify any families with two affected first-degree relatives [7].

In this paper, we use the updated Swedish Family-Cancer Database to analyse familial risk for the two most common histological types of eye cancer. The population base of the study is 10.5 million individuals, whose cancers were recorded in the Swedish Cancer Registry. To our knowledge, this is the first population-based nation-wide study on eye cancer.

Subjects and methods

Statistics Sweden maintains a 'Multigeneration Register' where children (offspring) born in Sweden in 1932 and

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later are registered with their parents (those pleading parenthood at birth) and are organized as families [12]. Information on the Database is also available at the Nature Genetics website as 'Supplementary information' [13]. The data on families and cancers have complete coverage, except for some groups of deceased offspring, which affect those born in the 1930s who died before 1991. This small group of offspring with missing links to parents has a negligible effect on the estimates of familial risk [14]. The 'Multigeneration Register' is linked by the individually unique national registration number to the Cancer Registry for the years 1958–2002. Cancer registration is considered currently to be close to 100% [15].

The site of cancer is registered on the basis of a four-digit diagnostic code according to ICD-7. For eye cancer (code 192), the histological types of melanoma (pathology anatomy code 176), retinoblastoma (436), unclassified (996) and glioma (471–476) are separated; however, glioma cases are so few that no results are reported. The following ICD-7 codes were pooled: 'upper aerodigestive tract' cancer codes 161 (larynx) and 140–148 (lip, mouth, pharynx), except for code 142 (salivary glands), and 'leukaemia' codes 204–207 (leukaemias), 208 (polycythemia vera) and 209 (myelofibrosis). Rectal cancer, ICD-7 code 154, was subdivided into anus (squamous cell carcinoma, 154.1) and mucosal rectum (154.0). In some anayses, leukaemias were divided into subtypes. Basal cell carcinoma of the skin is not registered in the Cancer Registry.

Standardized incidence ratios (SIRs) were used to measure cancer risks for offspring when their parents, siblings or both were diagnosed with specific cancers (that is using parents and siblings as probands). The reference rate was calculated for offspring whose parents/siblings had no specified cancer. SIR was the ratio of the observed to expected number of cases. The expected numbers were calculated from the standardized rates according to 5-year age group, sex, period, area (county) and socio-economic status. Confidence intervals (95% CI or 99% CI) were calculated assuming a Poisson distribution [16]. Follow-up was started for each offspring at birth, immigration or 1 January 1958, whichever came latest. Follow-up was terminated on the diagnosis of first cancer, death, emigration or the closing date of the study (31 December 2002). Risks for siblings were calculated using the cohort method, considering dependence between the pairs in the assessment of 95% CIs, as described elsewhere [17]. Some analyses were carried out in 'reverse order' using family members with eye cancer as probands and calculating SIRs for any cancer amongst the offspring.

Results

Of a total of 2594 parental and 1042 offspring eye cancers, 11 parent–offspring pairs (SIR for offspring eye cancer, 10.32) and six sibling pairs (16.59) were found with eye cancer (Table 1). Both of these SIRs were significant at a 1% level, which is shown as italic type in the tables. Offspring SIRs for eye cancer were also increased when parents were diagnosed with upper aerodigestive tract (1.90), salivary gland (4.38) and left-sided colon (1.82) cancers. When a sister was diagnosed with breast cancer, the SIR for eye cancer was 1.79.

The risk for ocular melanoma was not associated with any parental cancer (Table 2), although the associations with aerodigestive tract (2.05) and left-sided colon (1.83) cancers from Table 1 were of borderline significance. There were two patients diagnosed with ocular melanoma whose parents were also diagnosed with this neoplasm, giving a SIR of 3.90. There were three offspring with ocular melanoma when a parent was diagnosed with thyroid cancer. The SIR of 1.99 was not significant; however, all the affected parents were fathers and the SIR was 6.98 (95% CI, 1.32–20.65; the thyroid cancers were non-medullary). The risk for ocular melanoma was 1.76 when a sister was diagnosed with breast cancer. The age of onset for ocular melanoma or breast cancer did not deviate from the age of onset of these cancers in sibling pairs with other cancers. There was no association of ocular melanoma with cutaneous melanoma. The analysis was repeated in 'reverse order', that is parents with eye melanoma were probands and the SIR was calculated for any cancer in the offspring. The risk for leukaemia was increased in the offspring (SIR, 2.29; $n = 13$, 95% CI, 1.21–3.92). However, the cases presented with diverse subtypes of leukaemia.

The risk for retinoblastoma was 28.32 when a parent was diagnosed with any eye cancer (Table 3), and 899.98 ($n = 5$; 95% CI, 283.98–2216.99) when a parent was diagnosed with retinoblastoma. All offspring were diagnosed before the age of 4 years. In addition, parental small intestinal and rectal cancers and Hodgkin's disease were associated with retinoblastoma in the offspring. The offspring of the affected parents were diagnosed at ages ranging from 0 to 6 years. Sibling risks were also analysed, but only five siblings presented with diverse cancers other than retinoblastoma. 'Other' eye cancers were classified as pathology missing. They were increased to a SIR value of 25.90 when a parent was diagnosed with any eye cancer. Because even these cases were diagnosed before the age of 4 years, they were likely to be retinoblastomas. For 'other' and discordant sites, associations were observed for parental colon, particularly left-sided colon, and colorectal cancers and pancreatic cancers. However, the age at diagnosis for eye cancers was usually over 40 years, implying that they were not hereditary retinoblastomas. However, two offspring were diagnosed with eye cancers at a young age (4 and 10 years) and their parents were diagnosed with colon cancer also at a relatively young age (37 and 44 years). In these

Table 1 Standardized incidence ratio (SIR) for eye cancer in offspring by familial cancer

Familial site	Parent			Sibling		
	Observed	SIR	95% CI	Observed	SIR	95% CI
Upper aerodigestive tract	16	**1.90**	1.08–3.09	3	1.94	0.37–5.75
Salivary gland	4	**4.38**	1.14–11.34	0		
Stomach	23	1.32	0.83–1.98	1	0.89	0.00–5.08
Colon	36	1.36	0.95–1.88	1	0.36	0.00–2.05
Colon (right-sided)	12	0.97	0.50–1.69	0		
Colon (left-sided)	18	**1.82**	1.07–2.88	0		
Rectum	17	1.11	0.64–1.78	1	0.53	0.00–3.04
Colorectum	53	1.28	0.96–1.68	2	0.45	0.04–1.66
Liver	14	1.27	0.69–2.14	0		
Pancreas	13	1.19	0.63–2.04	3	3.03	0.57–8.97
Lung	23	0.90	0.57–1.35	3	0.79	0.15–2.35
Breast	41	1.00	0.71–1.35	25	**1.79**	1.16–2.65
Cervix	9	1.13	0.51–2.15	4	1.70	0.44–4.39
Endometrium	10	1.06	0.51–1.96	4	1.93	0.50–4.99
Ovary	4	0.46	0.12–1.20	1	0.42	0.00–2.44
Prostate	59	1.18	0.90–1.53	4	0.95	0.25–2.45
Kidney	6	0.51	0.19–1.13	2	1.10	0.10–4.05
Urinary bladder	16	0.94	0.54–1.53	1	0.42	0.00–2.43
Melanoma	12	1.23	0.63–2.16	5	1.07	0.34–2.52
Skin	9	0.71	0.32–1.36	1	0.75	0.00–4.29
Eye	11	**10.32**	5.12–18.52	6	**16.59**	5.97–36.35
Nervous system	19	**1.79**	1.08–2.80	5	1.14	0.36–2.67
Thyroid gland	4	1.31	0.34–3.39	1	0.79	0.00–4.52
Endocrine glands (other)	4	0.65	0.17–1.69	3	1.45	0.27–4.29
Non-Hodgkin's lymphoma	9	0.88	0.40–1.68	5	1.86	0.59–4.38
Hodgkin's disease	5	2.67	0.84–6.29	1	1.10	0.00–6.31
Myeloma	7	1.29	0.51–2.66	0		
Leukaemia	11	1.09	0.54–1.95	3	1.31	0.25–3.88
Any	309	1.10	0.98–1.23	39	1.06	0.75–1.45

CI, confidence interval. Bold type, 95% CI does not include 1.00.

Table 2 Standardized incidence ratio (SIR) for eye melanoma in offspring by familial cancer

Familial site	Parent			Sibling		
	Observed	SIR	95% CI	Observed	SIR	95% CI
Upper aerodigestive tract	10	2.05	0.97–3.78	2	1.97	0.19–7.25
Salivary gland	2	4.04	0.38–14.87	0		
Stomach	11	0.99	0.49–1.78	0		
Colon	20	1.25	0.76–1.93	1	0.54	0.00–3.11
Colon (right-sided)	6	0.79	0.28–1.72	0		
Colon (left-sided)	11	1.83	0.91–3.29	0		
Rectum	5	0.54	0.17–1.28	1	0.80	0.00–4.57
Colorectum	25	1.01	0.65–1.49	2	0.68	0.06–2.51
Liver	9	1.32	0.60–2.52	0		
Pancreas	4	0.60	0.16–1.54	2	3.04	0.29–11.19
Lung	12	0.80	0.41–1.41	3	1.17	0.22–3.47
Breast	18	0.84	0.50–1.33	16	**1.76**	1.00–2.87
Cervix	2	0.46	0.04–1.70	4	2.81	0.73–7.27
Endometrium	7	1.27	0.50–2.63	2	1.43	0.13–5.26
Ovary	2	0.41	0.04–1.51	0		
Prostate	41	1.37	0.99–1.87	3	1.03	0.19–3.06
Kidney	4	0.58	0.15–1.51	1	0.87	0.00–5.01
Urinary bladder	11	1.10	0.54–1.97	0		
Melanoma	3	0.68	0.13–2.02	3	1.05	0.20–3.11
Skin	4	0.51	0.13–1.33	1	1.13	0.00–6.48
Eye melanoma	2	3.90	0.37–14.32	0		
Nervous system	10	1.86	0.89–3.44	1	0.42	0.00–2.39
Thyroid gland	3	1.99	0.38–5.90	0		
Endocrine glands (other)	1	0.31	0.00–1.78	2	1.56	0.15–5.72
Non-Hodgkin's lymphoma	5	0.88	0.28–2.07	2	1.21	0.11–4.45
Hodgkin's disease	2	2.14	0.20–7.85	0		
Myeloma	5	1.53	0.48–3.60	0		
Leukaemia	7	1.19	0.47–2.47	2	1.71	0.16–6.31
Any	157	1.00	0.85–1.17	20	0.89	0.54–1.38

CI, confidence interval. Bold type, 95% CI does not include 1.00.

Table 3 Standardized incidence ratio (SIR) for retinoblastoma and undifferentiated eye cancers in offspring by parental cancer

Familial site	Retinoblastoma			Other		
	Observed	SIR	95% CI	Observed	SIR	95% CI
Upper aerodigestive tract	2	2.16	0.20–7.93	3	1.98	0.37–5.85
Salivary gland	1	8.07	0.00–46.28	1	5.93	0.00–33.97
Stomach	3	2.96	0.56–8.77	6	1.71	0.62–3.75
Small intestine	2	**11.05**	1.04–40.64	0		
Colon	1	0.44	0.00–2.52	10	2.01	0.96–3.71
Colon (right-sided)	0			3	1.27	0.24–3.77
Colon (left-sided)	0			6	**3.23**	1.16–7.07
Rectum	5	**3.58**	1.13–8.43	2	0.70	0.07–2.59
Colorectum	6	1.64	0.59–3.60	12	1.56	0.80–2.73
Liver	3	3.84	0.72–11.38	1	0.47	0.00–2.70
Pancreas	1	1.19	0.00–6.80	8	**3.78**	1.61–7.49
Lung	5	1.79	0.56–4.20	3	0.67	0.13–1.98
Breast	6	0.91	0.33–2.00	10	1.43	0.68–2.64
Cervix	1	0.88	0.00–5.04	2	1.48	0.14–5.45
Endometrium	0			1	0.58	0.00–3.35
Ovary	0			1	0.65	0.00–3.72
Prostate	3	0.66	0.13–1.97	6	0.64	0.23–1.41
Kidney	0			1	0.46	0.00–2.64
Urinary bladder	1	0.60	0.00–3.43	3	0.97	0.18–2.86
Melanoma	5	2.31	0.73–5.44	2	1.31	0.12–4.83
Skin	2	2.11	0.20–7.77	1	0.42	0.00–2.38
Eye	4	**28.32**	7.37–73.23	5	**25.90**	8.17–60.93
Nervous system	3	1.64	0.31–4.85	3	1.68	0.32–4.97
Thyroid gland	0			1	1.92	0.00–11.03
Endocrine glands (other)	1	1.05	0.00–6.00	0		
Non-Hodgkin's lymphoma	1	0.75	0.00–4.29	2	1.11	0.10–4.08
Hodgkin's disease	3	**9.22**	1.74–27.30	0		
Myeloma	0			2	1.89	0.18–6.96
Leukaemia	1	0.93	0.00–5.31	2	1.06	0.10–3.91
Any	47	1.35	0.99–1.79	57	1.14	0.86–1.47

CI, confidence interval. Bold type, 95% CI does not include 1.00.

two families, no other family member was diagnosed with cancer.

Discussion

To our knowledge, this is the first analytical epidemiological study on familial risks in eye cancers. The familial risk for retinoblastoma was high, as expected. Unfortunately, no data were available on the laterality of the retinoblastoma cases. Why the parents of children with retinoblastoma appeared to be at risk of small intestinal and rectal cancers and Hodgkin's disease is not readily explainable, because these are not typical cancers found as second tumours in *RB1* mutation carriers [2,3]. Some of these associations may be due to chance, but it is noteworthy that the SIRs were remarkably high: 11.05 for small intestinal tumours, 3.58 for rectal cancer and 9.22 for Hodgkin's disease. Because the children were diagnosed with a typical early-onset retinoblastoma before the age of 4 years (one offspring at an age of 6 years), it is likely that they were either born to a mutation carrier showing no disease or they acquired a new mutation [18]. The parents to these children were diagnosed in middle or late middle age, past the reproductive period, and it is not obvious why a new mutation in the parental germline, if any, would be related to the neoplasms diagnosed later. Unclassified eye cancers in the category 'other' also contained parents and offspring with concordant retinoblastoma, and they were probably also hereditary cases.

According to a recent review of the global literature on ocular melanoma, 71 families have been described, most containing two affected individuals [19]. This review made no statements on the occurrence of associated tumours in the families of probands. In the present study, ocular melanoma was detected in two parent–offspring pairs, but the SIR of 3.90 was not significant. Parental upper aerodigestive tract, left-sided colon and male non-medullary thyroid cancers showed an association (some with a borderline significance) with ocular melanoma, but, in the absence of other supporting evidence, this needs to be regarded as tentative. In the 'reverse order' analysis, the SIR for leukaemia was increased when parents were diagnosed with eye melanoma. However, no particular subtype of leukaemia appeared to explain this association, reducing its biological plausibility. There was no evidence for the association of ocular melanoma with cutaneous melanoma. The previously noted association with breast cancer was confirmed [7] and, in the present dataset, the association was only amongst siblings, not amongst parents and offspring. As no shared environmental risk factors for ocular melanoma and breast cancer are known, the high sibling risk, compared with the parent–offspring risk, suggests a recessive mode of inheritance. Together with mutation analysis, these data

provide evidence against the role of the dominantly acting *BRCA2* in the observed aggregation [8]. In attempts to characterize the putative susceptibility genes, the possible recessive mode of action needs to be considered.

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